

5

**CLAIMS**

What is Claimed Is:

- 10 1.) An isolated nucleic acid derived from a human gene encoding a protein selected from a member of the group consisting of aminopeptidase P protein (XPNPEP2), bradykinin receptor B1 protein (BDKRB1), tachykinin receptor 1 protein (TACR1), C1 esterase inhibitor protein (C1NH), kallikrein 1 protein (KLK1), bradykinin receptor B2 protein (BDKRB2), angiotension converting enzyme 2 protein (ACE2), and  
15 protease inhibitor 4 protein (PI4), wherein said nucleic acid comprises at least one polymorphic position.
- 2.) The isolated nucleic acid of claim 1 wherein said at least one polymorphic position for each said gene is a polymorphic position specified in Table V, or complement thereof.
- 20 3.) The isolated nucleic acid of claim 2 wherein the sequence at said at least one polymorphic position is depicted in a nucleic acid sequence selected from the group consisting of SEQ ID NO: 163 to 288; 643 to 706; and 910 to 961, and 1574 to 1575, or complement thereof.
- 25 4.) The isolated nucleic acid of claim 3 wherein said at least one polymorphic position resides in a non-coding position within the genomic sequence of said gene.
- 5.) The isolated nucleic acid of claim 3 wherein said at least one polymorphic position resides in a coding position within the genomic sequence of said gene.
- 30 6.) The isolated nucleic acid of claim 5 wherein said at least one polymorphic position residing in a coding position results in a missense mutation of the translated product of said gene.
- 7.) The isolated nucleic acid of claim 5 wherein said at least one polymorphic position residing in a coding position results in a silent  
35 mutation of the translated product of said gene.

- 5           8.)    The isolated nucleic acid of claim 4 wherein said at least one polymorphic position residing in a non-coding position resides within the untranslated region of said gene.
- 9.)    The isolated nucleic acid of claim 4 wherein said at least one polymorphic position residing in a non-coding position resides within
- 10           an intronic region of said gene.
- 10.)   The isolated nucleic acid of claim 8 wherein said at least one polymorphic position is selected from the group consisting of:
- a.) 62738 of the human bradykinin receptor B2 genomic sequence;
- 15               b.) 4627 of the human kallikrein 1 genomic sequence; and
- c.) 74651 of the human aminopeptidase P genomic sequence.
- 11.)   The isolated nucleic acid of claim 10 wherein said at least one polymorphic position is selected from the group consisting of:
- a.) 62738T of the human bradykinin receptor B2 genomic
- 20               sequence;
- b.) 62738A of the human bradykinin receptor B2 genomic sequence;
- c.) 4627C of the human kallikrein 1 genomic sequence;
- d.) 4627T of the human kallikrein 1 genomic sequence;
- 25               e.) 74651C of the human aminopeptidase P genomic sequence; and
- f.) 74651T of the human aminopeptidase P genomic sequence.
- 12.)   The isolated nucleic acid molecule according to claim 11, wherein said nucleic acid sequence is at least 30 nucleotides in length.
- 30           13.)   The isolated nucleic acid molecule according to claim 11, wherein said nucleic acid sequence is at least 40 nucleotides in length.
- 14.)   A probe that hybridizes to a polymorphic position defined in claim 2.
- 15.)   The probe of claim 14 wherein said probe is at least 15 nucleotides in length.
- 35           16.)   The probe of claim 15 wherein a central position of the probe aligns with said polymorphic position.

- 5           17.)   The probe of claim 15 wherein the 3' end of the primer aligns with said polymorphic position.
- 18.)   A method of analyzing at least one nucleic acid sample, comprising the steps of (1) obtaining said nucleic acid sample from one or more individuals; and (2) determining the nucleic acid sequence at one or
- 10           more polymorphic positions in a gene encoding a protein selected from the group consisting of aminopeptidase P protein (XPNPEP2), bradykinin receptor B1 protein (BDKRB1), tachykinin receptor 1 protein (TACR1), C1 esterase inhibitor protein (C1NH), kallikrein 1 protein (KLK1), bradykinin receptor B2 protein (BDKRB2),
- 15           angiotension converting enzyme 2 protein (ACE2), and protease inhibitor 4 protein (PI4).
- 19.)   The method according to claim 18, further comprising the steps of (3) testing each individual for the presence of a disease phenotype; and (4) correlating the presence of the disease phenotype with the sequence at
- 20           said one or more polymorphic positions.
- 20.)   The method according to claim 19, wherein said one or more polymorphic position of said nucleic acid sequence is a polymorphic position specified in Table V for said gene.
- 21.)   The method according to claim 20, wherein the nucleic acid sequence at said one or more polymorphic position is depicted in a nucleic acid
- 25           sequence selected from the group consisting of SEQ ID NO:163 to 288; 643 to 706; and 910 to 961, and 1574 to 1575, or complement thereof.
- 22.)   A method of constructing haplotypes using the isolated nucleic acids of claim 1, comprising the step of grouping at least two said nucleic acids.
- 30           23.)   The method according to claim 22 further comprising the step of using said haplotypes to identify an individual for the presence of a disease phenotype, and correlating the presence of the disease phenotype with said haplotype.
- 35           24.)   The method according to claim 19 further comprising the step of quantifying the nucleic acid sample comprising the polymorphic base.

- 5           25)   The method according to claim 21 or 23 wherein the disease phenotype is angioedema or an angioedema-like disorder.
- 26)   The method according to claim 25 wherein the polymorphic position is a member of the group consisting of:
- 10               a.)    62738 of the human bradykinin receptor B2 genomic sequence;
- b.)    4627 of the human kallikrein 1 genomic sequence; and
- c.)    74651 of the human aminopeptidase P genomic sequence.
- 15           27)   The isolated nucleic acid of claim 26 wherein the sequence at the polymorphic position is a member of the group consisting of:
- a.)    62738T of the human bradykinin receptor B2 genomic sequence;
- b.)    62738A of the human bradykinin receptor B2 genomic sequence;
- 20           c.)    4627C of the human kallikrein 1 genomic sequence;
- d.)    4627T of the human kallikrein 1 genomic sequence;
- e.)    74651C of the human aminopeptidase P genomic sequence; and
- 25           f.)    74651T of the human aminopeptidase P genomic sequence.
- 28)   A method for identifying an individual at risk of developing a disorder upon administration of a pharmaceutically acceptable amount of an ACE inhibitor and/or vasopeptidase inhibitor comprising the steps of
- 30               a.) obtaining nucleic acid sample(s) from said individual;
- b.) amplifying one or more sequences from said sample(s) using appropriate PCR primers for amplifying across at least one polymorphic position;
- c.) comparing said at least one polymorphic position with a known data set; and
- 35           d.) determining whether the result correlates with an increased or decreased risk for developing a disorder.

- 5           29) The method according to claim 28 wherein said at least one polymorphic position is selected from the group consisting of:
- a.) 62738 of the human bradykinin receptor B2 genomic sequence;
- b.) 4627 of the human kallikrein 1 genomic sequence; and
- 10           c.) 74651 of the human aminopeptidase P genomic sequence.
- 30) The isolated nucleic acid of claim 29 wherein said at least one polymorphic position is selected from the group consisting of:
- a.) 62738T of the human bradykinin receptor B2 genomic sequence;
- 15           b.) 62738A of the human bradykinin receptor B2 genomic sequence;
- c.) 4627C of the human kallikrein 1 genomic sequence;
- d.) 4627T of the human kallikrein 1 genomic sequence;
- 20           e.) 74651C of the human aminopeptidase P genomic sequence; and
- f.) 74651T of the human aminopeptidase P genomic sequence.
- 31) The method of claim 30 wherein the disorder is angioedema or an angioedema-like disorder.
- 25           32) A library of nucleic acids, each of which comprises one or more polymorphic positions within a gene encoding a human protein selected from the group consisting of aminopeptidase P protein (XPNPEP2), bradykinin receptor B1 protein (BDKRB1), tachykinin receptor 1 protein (TACR1), C1 esterase inhibitor protein (C1NH), kallikrein 1 protein (KLK1), bradykinin receptor B2 protein (BDKRB2), angiotension converting enzyme 2 protein (ACE2), and protease inhibitor 4 protein (PI4), wherein said polymorphic positions
- 30           are selected from a group consisting of the polymorphic positions provided in Table V.
- 35

- 5            33)    The library of nucleic acids of claim 32 wherein the sequence at said polymorphic position is selected from the group consisting of the sequences provided in Table V.
- 34)    The library according to claim 33 wherein the polymorphic position is a member of the group consisting of:
- 10                a.)    62738 of the human bradykinin receptor B2 genomic sequence;
- b.)    4627 of the human kallikrein 1 genomic sequence; and
- c.)    74651 of the human aminopeptidase P genomic sequence.
- 15            35)    The library according to claim 34 wherein the sequence at the polymorphic position is a member of the group consisting of:
- a.)    62738T of the human bradykinin receptor B2 genomic sequence;
- b.)    62738A of the human bradykinin receptor B2 genomic sequence;
- 20                c.)    4627C of the human kallikrein 1 genomic sequence;
- d.)    4627T of the human kallikrein 1 genomic sequence;
- e.)    74651C of the human aminopeptidase P genomic sequence; and
- 25                f.)    74651T of the human aminopeptidase P genomic sequence.
- 36)    The library according to claim 35 wherein said library of isolated sequences represents the complimentary sequence of said sequences.
- 37)    A kit for identifying an individual at risk of developing a disorder upon administration of a pharmaceutically acceptable amount of an ACE inhibitor and/or vasopeptidase inhibitor, said kit comprising
- 30                    i.)    sequencing primers, and
- ii.)    sequencing reagents,
- wherein said primers are primers that hybridize to at least one polymorphic position in a human gene selected from the group consisting of aminopeptidase P protein (XPNPEP2), bradykinin
- 35

- 5                   receptor B1 protein (BDKRB1), tachykinin receptor 1 protein (TACR1), C1 esterase inhibitor protein (C1NH), kallikrein 1 protein (KLK1), bradykinin receptor B2 protein (BDKRB2), angiotension converting enzyme 2 protein (ACE2), and protease inhibitor 4 protein (PI4).
- 10           38)   The kit according to claim 37 wherein said polymorphic positions are selected from a group consisting of the polymorphic positions provided in Table V.
- 39)   The kit according to claim 38 wherein the polymorphic position is a member of the group consisting of:
- 15                   a.)    62738 of the human bradykinin receptor B2 genomic sequence;
- b.)    4627 of the human kallikrein 1 genomic sequence; and
- c.)    74651 of the human aminopeptidase P genomic sequence.
- 20           40)   The kit according to claim 39 wherein the sequence at the polymorphic position is a member of the group consisting of:
- a.)    62738T of the human bradykinin receptor B2 genomic sequence;
- b.)    62738A of the human bradykinin receptor B2 genomic sequence;
- 25                   c.)    4627C of the human kallikrein 1 genomic sequence;
- d.)    4627T of the human kallikrein 1 genomic sequence;
- e.)    74651C of the human aminopeptidase P genomic sequence; and
- 30                   f.)    74651T of the human aminopeptidase P genomic sequence.
- 41)   The kit according to claim 40 wherein said primer(s) hybridizes immediately adjacent to said polymorphic positions.

- 5           42)    The kit according to claim 41 wherein said primer(s) hybridizes to said polymorphic positions such that the central position of the primer aligns with the polymorphic position of said gene.
- 43)    The method according to claim 28 further comprising the step of  
10           subjecting the product(s) of said amplification to a genetic bit analysis (GBA) reaction.
- 44)    A method for identifying an individual at risk of developing a disorder upon administration of a pharmaceutically acceptable amount of an ACE inhibitor and/or vasopeptidase inhibitor comprising the steps of
- a.)    obtaining a nucleic acid sample(s) from said individual;  
15           b.)    determining the nucleotide present at least one polymorphic position,  
              c.)    comparing said at least one polymorphic position with a known data set; and  
              d.)    determining whether the result correlates with an  
20           increased or decreased risk for developing a disorder.
- 45)    The method according to claim 44 wherein said at least one polymorphic position is selected from the group consisting of:
- a.)    62738 of the human bradykinin receptor B2 genomic sequence;  
25           b.)    4627 of the human kallikrein 1 genomic sequence; and  
              c.)    74651 of the human aminopeptidase P genomic sequence.
- 46)    The isolated nucleic acid of claim 45 wherein said at least one polymorphic position is selected from the group consisting of:
- 30           a.)    62738T of the human bradykinin receptor B2 genomic sequence;  
              b.)    62738A of the human bradykinin receptor B2 genomic sequence;  
              c.)    4627C of the human kallikrein 1 genomic sequence;  
35           d.)    4627T of the human kallikrein 1 genomic sequence;



- 5 e.) 74651C of the human aminopeptidase P genomic sequence; and
- f.) 74651T of the human aminopeptidase P genomic sequence.
- 10 47) The method of claim 46 wherein the disorder is angioedema or an angioedema-like disorder.
- 48) A method for genotyping an individual comprising the steps of
- a.) obtaining a nucleic acid sample(s) from said individual;
- b.) determining the nucleotide present at least one polymorphic position, and
- 15 c.) comparing said at least one polymorphic position with a known data set.
- 49) The method according to claim 48 wherein said at least one polymorphic position is selected from the group consisting of:
- a.) 62738 of the human bradykinin receptor B2 genomic sequence;
- 20 b.) 4627 of the human kallikrein 1 genomic sequence; and
- c.) 74651 of the human aminopeptidase P genomic sequence.
- 50) The isolated nucleic acid of claim 49 wherein said at least one polymorphic position is selected from the group consisting of:
- 25 a.) 62738T of the human bradykinin receptor B2 genomic sequence;
- b.) 62738A of the human bradykinin receptor B2 genomic sequence;
- 30 c.) 4627C of the human kallikrein 1 genomic sequence;
- d.) 4627T of the human kallikrein 1 genomic sequence;
- e.) 74651C of the human aminopeptidase P genomic sequence; and
- 35 f.) 74651T of the human aminopeptidase P genomic sequence.